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EXAMINER	
PRIEBE, SCOTT DAVID	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,644	LIU ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004 and 18 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15-35,46-53 and 106-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-35,46-53 and 106-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Sequence Compliance

The submission of the substitute Sequence Listing filed 1/18/05 is acknowledged. However, the submission does not fully comply with 37 CFR §§1.821-1.825. Specifically, the submission does not include the statement required under §1.821(g) that the submission includes no new matter. Providing the required statement, which identifies the paper copy and CRF of the Sequence Listing by their 1/18/05 filing date, would be remedial.

Election/Restrictions

Applicant's election without traverse of group I, claims 1-35, 46-54, and 96-105 in the reply filed on 9/27/04 is acknowledged. Claims 36-45, and 55-95 directed to non-elected inventions have been cancelled.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claim 34, for example, specifies that the regulatory elements from the *C. elegans* vap-2 gene would direct expression in pharyngeal gland cells, which is new matter for

the reasons set forth below, or in amphid sheath cells. While the embodiment directed to expression in amphid sheath cells has support in original claims 101-105, the specification provides no antecedent basis for this embodiment, i.e. the specification itself does not mention that the vap-2 gene is expressed in amphid sheath cells or that its promoter region would direct expression in amphid sheath cells.

Claim Rejections - 35 USC § 112

Claims 1-13, 15-35, and 46-53 remain rejected and claims 106-142 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action of 3/23/04 and the additional reasons set forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 46 (and their dependent claims 2-13, 15-35, 47-53, 114) have been amended to limit the nematode to *C. elegans* and to limit expression of the detectable marker to a pharyngeal gland cell or amphid sheath cell of the *C. elegans*. However, the regulatory region recited in the claims remains generic with respect to the nematode from which the region is isolated and with respect to whether the endogenous gene from which the regulatory element is derived is normally expressed in a pharyngeal gland cell or amphid sheath cell of *C. elegans* or another nematode.

The juxtaposition of specific limitations with respect to the nematode and expression of the detectable marker in certain cells and the generic limitation with regard to the identity of the

regulatory region in claims 1 and 46 (and their dependent claims) introduces new matter. Also, the specification does not disclose in general that regulatory elements from members of the *C. elegans vap* gene family (claims 32 and 35) would direct expression of a transgene in a pharyngeal gland cell or amphid sheath cell of *C. elegans*, or that regulatory elements from the *C. elegans* vap-1 or vap-2 genes would direct expression in a pharyngeal gland cell, as in claims 33 and 35. This also introduces new matter. Applicant (p. 14, Reply of 9/27/04) indicates that the amendments to claims 1 and 46 would be discussed, but then fails to indicate where the original disclosure supports the embodiments now being claimed. The Examiner could find no support for a generic regulatory region in the context of a transgenic *C. elegans* where the detectable marker was expressed specifically in a pharyngeal gland cell or an amphid sheath cell. As described in the specification at ¶ 73, Examples 4, 8 and 9, and original claims 15 to 18, when the nematode is *C. elegans*, the regulatory region is from a gene encoding a secreted product of *C. elegans*.

Apart from the issue of new matter with respect to claims 1 and 46, the specification identifies only one regulatory element as mediating expression of a detectable marker in a pharyngeal gland cell or an amphid sheath cell in *C. elegans*. The regulatory element directs expression only in an amphid sheath cell, is present in a 6.5 kb fragment of genomic DNA in the vicinity of the *C. elegans* vap-1 gene that includes 4.8 kb upstream of the vap-1 start codon, and is not characterized with respect to its sequence. Original claims 101-105 indicates that an uncharacterized regulatory element from the *C. elegans* vap-2 gene would also direct expression in an amphid sheath cell in *C. elegans*, but the specification does not teach this. The specification

does not identify a regulatory element, either by its sequence or by reference to a gene from which it can be isolated, that would mediate expression in a pharyngeal gland cell in *C. elegans*.

The specification does not disclose structural characteristics by which one would identify members of a genus of regulatory element from a gene encoding a nematode secretory product that direct expression of a detectable marker (or any other heterologous polypeptide) specifically in a pharyngeal gland cell or amphid sheath cell of a transgenic *C. elegans*. It also does not describe sufficient numbers of species embraced by such a genus. Only one confirmed regulatory element (from the *C. elegans* vap-1 gene) and one unconfirmed regulatory element (from *C. elegans* vap-2 gene) is described that would direct expression in an amphid sheath cell of *C. elegans*, and no regulatory elements are disclosed that would direct expression in a *C. elegans* pharyngeal gland cell.

One may presume that regulatory elements from other *C. elegans* genes encoding secretory products would direct expression in a pharyngeal gland cell or amphid sheath cell of a transgenic *C. elegans* exist, and the specification describes methods by which one could identify endogenous secretory products that are secreted from a pharyngeal gland cell or amphid sheath cell in *C. elegans* or the analogous organs in other nematodes. However, such disclosure is not sufficient to describe a DNA, either specifically or generically; it does not demonstrate possession of such products. The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference

to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

Claims 106 and 110 (and their dependent claims) are directed to methods of expressing polynucleotides in *C. elegans* that are operably linked to regulatory regions of a vap-1 or vap-2 gene. The claims are generic to the cell in which the polynucleotide is expressed. These claims are said to be supported by original claims 100 and 105. However, original claims 100 and 105 limited the expression specifically in amphid sheath cells, not in *C. elegans* generically. The examples pertaining to use of the vap-1 regulatory region describe only expression in amphid sheath cells. Example 6 does not describe using the vap-2 regulatory region for expression of a generic polypeptide, and does not identify the cells in which the detectable marker was expressed. Thus these claims are directed to a generic method that is broader than originally described, and therefore incorporate new matter.

Claim 115 is directed to a method of making a transgenic *C. elegans* comprising identifying a *C. elegans* homolog of a parasitic nematode secretory protein that is expressed in a pharyngeal gland cell, and amphidial gland cell, "or both" of the parasitic nematode, then introducing a transgene into *C. elegans* that comprises a detectable marker operably linked to a DNA element "whose sequence comprises a sequence located up to 10 kb immediately upstream of the start codon of the gene that encodes the *C. elegans* homolog". Claims 116-123 are directed to transgenic *C. elegans* made by the method of claim 115. The latter phrase is also recited in claim 116 and in claims 117 and 118, except "10" is replaced with "8" or "6." Claim 125 is similar to claim 115, except the secretory protein is identified in *C. elegans*. Claims 125-130 are directed to a transgenic nematode, generically, not a transgenic *C. elegans* specifically, where the coding sequence for a detectable marker is operably linked to a DNA element "whose sequence comprises a sequence located up to ... kb immediately upstream of the start codon" of any *C. elegans* gene encoding a secretory protein. None of these claims requires that the second DNA sequence includes a regulatory element.

Recitation of "or both" referring to expression in pharyngeal gland cells and amphidial gland cells is new matter. None of the passages in the specification that Applicant points to for support of these claims describes this limitation. While the original specification describes identifying secretory proteins expressed in either of these glands in parasitic nematodes, e.g. ¶ 0104, or in the corresponding glands of *C. elegans*, it does not describe or allude to a secretory protein expressed in both glands.

With respect to the limitation "DNA element whose sequence comprises a sequence located up to ... kb immediately upstream of the start codon," this limitation does not require

that the DNA element comprise sequences that extend upstream from the start codon for 10/8/6 kb, but only that the element comprise a sequence of unspecified length from the region bounded by the start codon and a point 10/8/6 kb upstream of the start codon. Applicant points to ¶126 as supporting this limitation. However, ¶126 describes where the promoter of a gene may be found relative to the start codon of a gene, and teaches that the transgene will include up to 2/4/6/8/10/20 kb of genomic DNA upstream of the start codon. First, this disclosure teaches that this sequence will contain a promoter (regulatory elements), and second that the sequence will include all of the genomic DNA from the start codon and upstream sequences extending for 2, 4, 6, etc. kilobases. It does not suggest that the promoter will be absent or that the sequence will be located within this region, for example a sequence starting at 9.6 kb upstream and ending at 8.3 kb upstream of the start codon. Applicant also points to ¶129 for support, specifically with regard to *C. elegans* secreted proteins. However, this paragraph teaches that the "reporter transgenes comprise a regulatory element comprising between 0 and 10 kB of *C. elegans* genomic DNA sequence immediately 5' from the start codon." As with ¶126, this indicates that a regulatory element is present and the sequence will include all of the genomic DNA from the start codon to 0 to 10 kB upstream. It is noted that this teaching makes no sense with respect to the lower limit, between the start codon and 0kB upstream of the start codon is no sequence at all, at most this would consist of a phosphodiester bond, i.e. such a transgene would be promoterless and would not express. Consequently, the limitation "DNA element whose sequence comprises a sequence located up to ... kb immediately upstream of the start codon" is not supported by the original specification and is new matter.

Applicant's arguments filed 9/27/04 have been fully considered but they are not persuasive. Applicant argues that it is not necessary for the specification to list all species readable on a generic invention in order to satisfy the written description requirement. However, this is true where a specification has described a sufficient number of species in order to adequately describe the genus. However, where the specification does not describe a sufficient number of species, there is not adequate support for a generic claim. See *Amgen v. Chugai,* 18 USPQ2d 1016, 1027 ((Fed. Cir. 1991), just after the *Robins* citation. Applicant has failed to indicate how the disclosure of one (from vap-1) and at most two (and from vap-2) species of promoter region from *C. elegans* that direct expression in amphid sheath cells demonstrates possession of all nematode or *C. elegans* regulatory elements from genes encoding secretory products, particularly when no structure-function detail for any such regulatory element in the specification and when one expects the different members of this genus to vary significantly with respect to their structure, even between genes encoding members of the venom allergen protein family. For example, Gao et al. (Intl. J. Parasitol. 31: 1617-1625, 2001) teaches that Hg-Vap-1 and Hg-Vap-2 are expressed in the oesophageal glands of *Heterodera glycines*, not the pharyngeal glands and not the amphidial glands, where its homologs ASP-1 of *Ancyclostoma canimum* and vap-1 of *C. elegans* are expressed. As indicated in ¶76 of the specification, oesophageal glands are distinct from pharyngeal glands. Gao further discloses a personal communication from A. Sluder, who is presumed to be instant inventor Ann Sluder, that one of two 2-domain *C. elegans vap* genes is expressed in amphid sheath cells and the second is expressed in excretory duct cells. See page 1624 of Gao. One can infer from these results that in general the promoters of different nematode VAP protein genes do not share structural and

functional features, because structural elements in promoters are what mediate cell-specific expression. If genes are expressed in different cells, then the regulatory elements responsible for the cell-specific expression are different for each.

With respect to the disclosure of the personal communication from A. Sluder, instant examples 1 and 2 indicate that *C. elegans* has only two 2-domain vap proteins, vap-1 and vap-2, the remainder being 1-domain vap proteins. The report in Gao does not identify the specific 2-domain vap proteins communicated by A. Sluder. However in light of the specification, it is reasonable that the vap proteins mentioned in Gao may be vap-1 (amphid sheath) and vap-2 (excretory duct). If so, then claims requiring expression from a vap-2 promoter in pharyngeal gland cells or amphid sheath cells (e.g. claim 34) would be inoperative. Original claims 101-105 indicate that the vap-2 promoter is expressed in amphid sheath, although example 6 does not identify where the vap-2::GFP transgenes were expressed. The evidence presented in Gao is not conclusive as to the identity of the vap expressed in excretory duct cells. Consequently, there is insufficient evidence of record to sustain a rejection of such claims reciting vap-2 expression in pharyngeal gland cells or amphid sheath cells under 35 USC §101 or §112, 1st para. as being inoperative. Applicant is requested to provide clarification on this matter.

Applicant asserts it is not necessary to provide sequences of nematode regulatory elements to satisfy the written description requirement because "the necessary common features or attributes possessed by the genus are not in fact to be found in the sequences of the regulatory elements themselves but rather in the position of the regulatory elements with respect to coding sequences for nematode secretory products within the nematode genome". Applicant then points

to the specification for teaching that regulatory regions are to be found within 10 kb upstream of the start codon of a gene encoding a nematode secretory product.

In response, Applicant has provided no evidence to support this assertion. "Argument of counsel cannot take the place of evidence lacking in the record." *In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974). If the assertion were true, it would not matter what specific sequence was upstream of the start codon, any sequence would do. Applicant is respectfully referred to any textbook on molecular biology with regard to the sequence specificity of RNA polymerase binding sites (minimal promoter) and of cis-acting regulatory elements to which transcription factors bind. The polymerase binding site of most, if not all, eukaryotic genes is located in the first 50 nucleotides upstream of the start site of transcription. Most regulatory elements are found upstream of the polymerase binding site, how far upstream depends on the specific gene. Regulatory elements may also be found downstream of the transcriptional start site, even, albeit rarely, in the coding sequence. The function of the polymerase binding sequences and cis-acting regulatory sequences depend directly on the specific nucleotide sequences themselves, and often depend in part on the positions of the regulatory elements with respect to each other and the polymerase binding site. The position of the start codon provides only a rough approximation of where the promoter of a gene may be found, since the upstream untranslated sequences of an mRNA (region between the transcription start site and the start codon) may vary considerably in length between different genes.

That the regulatory region (promoter) of a gene is generally to be found within 10 kb of the start codon is a feature or attribute that is shared not only by genes encoding nematode secretory proteins, but by many genes from any organism. (It is noted that the regulatory region

of some genes may extend well upstream of 10 kb from the start site of transcription.) Therefore, the teaching that the promoter of a gene identified as encoding a secretory product can be found within 10 kb upstream of the start codon is not a characteristic or attribute of the regulatory elements required by the invention that distinguishes them from other regulatory elements outside the scope of the invention. Rather, this teaching relates more to a method for obtaining such regulatory elements for use in making the claimed invention. An adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method. What is required is a description of the nucleic acid itself. It is not sufficient to define DNA solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, *Fiers v. Revel*, *Fiddes v. Baird*, and *Regents of the Univ. Calif. v. Eli Lilly & Co.* The only regulatory regions adequately described in the instant specification are the regulatory region of the *C. elegans vap-1* gene, which, when in a transgene, directs expression in

amphid sheath cells of a transgenic *C. elegans*, and the regulatory region of the *C. elegans vap-2* gene, which, when in a transgene, directs expression in unspecified cells (possibly amphid sheath cells) of a transgenic *C. elegans*. There is no description of the regulatory elements responsible for the function of the regulatory region. Applicant argues that the claims do not require "narrowing down the regulatory element to a minimal region." While the claims embrace embodiments where a gene fragment comprising the regulatory element, they also embrace embodiments where the genomic sequence is narrowed down to the minimal sequence. Since the specification fails to identify the structural features of any such regulatory element, there is no way one can envision or recognize what such a minimal sequence would look like.

Applicant then relies upon *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). Applicant mischaracterizes *Enzo*. The court at 1614 found that the deposit of specific sequences was sufficient to meet the written description of the deposited sequence. The issue of whether the deposited sequences were sufficient to meet the written description for variants of the deposited sequences that shared the specified functional features was not decided by the court, but was remanded. Also, the issues of whether the deposited sequences or the deposited bacteria were sufficient to meet the written description for unrelated sequences isolated from the same bacterium and sharing the specified functional features were not decided by the court, but were remanded. See *Enzo* at 1615-1616. Applicant's subsequent arguments relying upon the mischaracterization of *Enzo* at pages 18 and 19 of the reply are therefore moot.

As part of this argument, Applicant refers to teachings in the specification (¶s 129 and 170) disclosing other *C. elegans* vap genes and *C. elegans* genes encoding other secretory

products. This disclosure is not relevant to the instant claims since the specification does not teach that these other genes are expressed in amphid sheath cells or pharyngeal gland cells.

Applicant argues that since the sequence of the *C. elegans* genome was known when the application was filed, and therefore the sequence of regulatory regions of genes encoding secretory products, the written description requirement is met. In response, Applicant has provided no evidence that the *C. elegans* sequence was known. However, even if this sequence was known, there is no evidence the identity of the various predicted coding sequences was known with respect to whether the predicted sequences encoded secretory products, much less which of these were located downstream of a regulatory region that would direct expression in a pharyngeal gland cell or amphid sheath cell. Without knowing what specific regulatory sequences provide the function of directing expression in an amphid sheath cell or pharyngeal cell, one would not be able to point to a particular sequence within the genomic sequence and know that it was a regulatory element that could be used in the claimed invention.

Applicant argues that Examples 4-9 demonstrate possession of the invention. However, these working examples were limited to the isolation of regulatory regions, not regulatory elements *per se* from the *C. elegans* vap-1 and vap-2 genes. The examples show that the vap-1 sequence would direct expression of the transgene in *C. elegans* amphid sheath cells, not in pharyngeal cells, and that the vap-2 sequence would direct expression of the transgene in some unspecified cells in *C. elegans*. As indicated above, it is unclear whether the vap-2 sequence directs expression in amphid sheath cells, and there is no mention in the specification that the vap-2 sequence directs expression in pharyngeal gland cells.

However, the originally files specification does provide an adequate written description of an embodiment where the nematode is *C. elegans* and the transgene comprises the regulatory region of *C. elegans* vap-1 and is expressed in amphid sheath cells. The disclosure of the primer sequences and strain of *C. elegans* that were used to isolate the vap-1 regulatory region provide sufficient written description for claims directed to this embodiment.

Applicant finally argues that the claims are directed to a genus of transgenic nematode comprising members of a genus of regulatory elements, and that *Fiddes* and *Lilly* do not apply. In response, the critical element of the claimed invention is the regulatory element, specifically from a gene encoding a nematode secretory protein, and specifically that directs expression in pharyngeal gland cells or amphidial gland or amphid sheath cells. One cannot possess or describe a genus of a combination, i.e. the transgenic nematode, comprising one member of a genus of particular subcombinations, i.e. the regulatory region, unless one is in possession of the genus of subcombination. By Applicant's logic here, while possession of only a sequence encoding bovine FGF would not adequately describe a coding sequence for a genus of FGF in *Fiddes*, it would have been adequate to support a claim to a host cell comprising the generic coding sequence in an expression vector.

Applicant's disclosure and the prior art show only that the regulatory elements required by the claims exist, and describe a potential method for isolating them. They do not show or describe what they are physically, such that one could distinguish between DNA that comprised the required regulatory element from DNA that did not. As indicated above, Gao shows that different nematode secretory products, even those within the VAP family, are produced in different types of cells, and hence must have different regulatory elements. There clearly is no

structure-function relationship between the secreted protein and the regulatory element that directs its expression. Knowing a protein is secreted does not tell one which type of cell secretes it, much less the identity of the regulatory element that directs its expression in a specific type of cell. Knowing that a protein is secreted in a specific cell tells one that a regulatory element exists that directs its expression in that cell, but does not tell one what that regulatory sequence is or place one in possession of DNA containing it. At best, it gives one a starting point for isolating it. However, an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Regents of the Univ. Calif. v. Eli Lilly & Co.*, for example.

Claims 1-13, 15-35, 46-53 remain rejected and claims 114-119 and 122-129 are rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 3/23/04, because the specification, while being enabling for a transgenic *C. elegans* where the transgene comprises the regulatory region of a *C. elegans* vap-1 gene or vap-2 gene and directs expression in amphid sheath cells, does not reasonably provide enablement for other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 33 and 34 are included in this rejection because the claims read on expression of the detectable marker in pharyngeal gland cells. Limiting claims 33 and 34 to expression in amphid sheath cells would overcome the rejection. However, as noted above, there is some

question as to whether the vap-2 regulatory sequence would in-fact direct expression in amphid sheath cells.

Applicant's arguments filed 9/27/04 have been fully considered but they are not persuasive. With the exception of claims 125-129, the rejected claims are directed to a transgenic *C. elegans*. Applicant has not addressed the grounds of rejection pertaining to making transgenic nematodes other than transgenic *C. elegans*.

Applicant argues that the specification teaches where regulatory elements may be found relative to start codons, and the claims do not require minimal regulatory sequences, i.e. larger genomic sequences comprising them can be used. In response, knowing that a promoter may be found upstream of a gene encoding a secretory product does not tell you how to make it or what it is. The invention does not require the secretory protein itself or its coding sequence to be used. One requires at minimum the regulatory elements that direct expression of the secretory product in amphid sheath cells or pharyngeal cells in order to make the invention. The regulatory element is the critical feature, and the specification does not disclose a genus of regulatory elements that would direct expression of a detectable marker in amphid sheath cells or pharyngeal gland cells. The specification describes two species of regulatory element that would direct expression of the marker in amphid sheath cells (from the *C. elegans* vap-1 and vap-2 genes), and no species of regulatory element that would direct expression in pharyngeal gland cells. The structure of these sequences is not provided, the only structural information disclosed is their size.

The examiner concurs that knowledge of the actual sequence of a regulatory region or the specific regulatory elements is not necessarily required for enablement. Enablement can be satisfied in other ways, such as by deposit of the sequences. However, Applicant has not

deposited any such sequences. The specification does enable one to make a sequence comprising a promoter from the *C. elegans vap-1* and *vap-2* genes by disclosure of PCR primer sequences and identification of the template DNA and size of the fragment one should obtain. However, the specification does not provide such guidance for other regulatory regions or promoters that would direct expression in either of the specified cells.

Applicant asserts (page 22) that "DNA sequences upstream of numerous genes encoding nematode secretory proteins or homologs thereof were known in the art as of the filing date of the application," but fails to provide any evidence to support this assertion. "Argument of counsel cannot take the place of evidence lacking in the record." *In re Scarbrough*, 182 USPQ 298, 302 (CCPA 1974). Even if the entire genomic sequence of a nematode were known, as has been alleged for *C. elegans*, one would still have to know how to analyze the sequence in order to identify regulatory elements that meet the claim limitations. Without knowing what specific sequences provide the function of directing expression in pharyngeal gland cells or amphid sheath cells, one would be unable to identify such sequences in a published sequence by a known structure-function relationship. One could perhaps guess that suitable promoter sequences would be upstream of the start codon of coding sequence of a protein known to be secreted from amphid sheath cells or pharyngeal cells in *C. elegans*, but Applicant has not pointed to where the specification identifies such secreted proteins. The specification does not teach that vap-1 and vap-2 are secreted from either of these cell types, although one of skill in the art may deem it likely that vap-1 is at least expressed in amphid sheath cells based on the results disclosed in the examples. As to whether vap-1 is actually expressed, and secreted, from amphid sheath cells, that would require experimental determination using non-transgenic *C. elegans*. At best, the

specification tells one what to look for in a suitable regulatory element, but does not teach one what it is generically or how to make it.

The claims embrace embodiments where only the minimal sequence is present in the transgene. Applicant takes issue with the Examiner's assertion that promoters have specific 5' and 3' boundaries. However, Applicant admits (bottom of page 22) that "it is clear that removal of certain sequences at either the 5' or 3' end of promoter regions can abrogate their function and that certain sequences lying outside promoter regions are not necessary for promoter activity." This is simply restates the Examiner's assertion in different language. Furthermore, Applicant admits that they "are not aware of a method that can unambiguously determine specific 5' and/or 3' boundaries of promoters". The specification also does not teach how the minimal sequence would be determined. The specification clearly fails to enable making such minimal regulatory sequences. However, given the disclosure of a vap-1 genomic fragment that contains the minimal sequence, it would have been routine in the art to narrow down or determine the minimal sequence if desired, e.g. by terminal deletion analysis.

The specification does not describe other promoters or regulatory elements of genes encoding nematode secretory products that would direct expression of a transgene in pharyngeal gland cells or amphid sheath cells. Although one of skill in this art would know such promoters must exist, a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the germ of an idea, as here with respect to a generic regulatory element that directs expression in specific cells, does not constitute an enabling disclosure. While every aspect of a generic claim need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the

skilled artisan to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement under 35 USC 112, first paragraph. When there is no disclosure of the specific starting materials or conditions under which the process can be carried out, there is a failure to meet the enablement requirement. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997). With the exception of the *C. elegans* vap-1 regulatory region, and possibly the *C. elegans* vap-2 regulatory region, the specification does not disclose the specific starting materials necessary to enable the breadth of the claims. Furthermore, relying on the vap-1 regulatory region (and possibly the vap-2 regulatory region) in order to enable a genus of regulatory elements that direct expression in amphid sheath cells is analogous to a single means claim, which has been held not to comply with the first paragraph of section 112. See *Fiers* at 1606. With respect to regulatory elements that direct expression in pharyngeal gland cells, the specification describes no means for doing so.

Claim Rejections - 35 USC § 102

Claims 125-128 are rejected under 35 U.S.C. 102(a) as being anticipated by Plenefisch et al. for the reasons of record applied to claims 1, 2, 5, 6, 10-12, 14-29, 46, 48-50, and 53-54 in the Office action of 3/23/04.

Applicant presents no arguments that apply to this new rejection. The claims do not require expression in any particular type of cell.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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